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09/480,236	01/10/2000	Mary Ellen Digan	4-31157A/USN	4092

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EXAMINER
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1644	17

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/480,236	Applicant(s) Digan et al.
	Examiner G.R. Ewoldt	Art Unit 1644

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *10/18/01 and 1/16/02*.

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-7, 9-16, and 29-34* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-7, 9-16, and 29-34* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)

16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *13*

18) ☐ Interview Summary (PTO-413) Paper No(s). _____

19) ☐ Notice of Informal Patent Application (PTO-152)

20) ☐ Other:

DETAILED ACTION

1. The request filed on 1/16/02 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/480,236 is acceptable and a CPA has been established. An action on the CPA follows. The unentered amendment, filed 10/18/01, has been entered.

2. Claims 1-7, 9-16, and 29-34 are pending and being acted upon.

3. The first line of the specification must be updated to indicate the status of prior application 09/236,968, converted to provisional application No. 60/266,285.

4. New corrected drawings must be filed with the changes incorporated therein, as set forth in the PTO Form 948, mailed 11/21/00. Identifying indicia, if provided, should include the title of the invention, inventor's name, and application number, or docket number (if any) if an application number has not been assigned to the application. If this information is provided, it must be placed on the front of each sheet and centered within the top margin. If corrected drawings are required in a Notice of Allowability (PTOL-37), the new drawings MUST be filed within the THREE MONTH shortened statutory period set for reply in the "Notice of Allowability." Extensions of time may NOT be obtained under the provisions of 37 CFR 1.136 for filing the corrected drawings after the mailing of a Notice of Allowability. The drawings should be filed as a separate paper with a transmittal letter addressed to the Official Draftsperson.

Corrections other than Informalities Noted by Draftsperson on form PTO-948. All changes to the drawings, other than informalities noted by the Draftsperson, MUST be made in the same manner as above except that, normally, a highlighted (preferably red ink) sketch of the changes to be incorporated into the new drawings MUST be approved by the examiner before the application will be allowed. No changes will be permitted to be made, other than correction of informalities, unless the examiner has approved the proposed changes.

Timing of Corrections. Applicant is required to submit acceptable corrected drawings <u>within the time period set in the Office action</u>. See 37 CFR 1.85(a). Failure to take corrective action within the set period will result in ABANDONMENT of the application.

5. The abstract of the disclosure is objected to because of the use of legal phraseology such as "said". Correction is required. See MPEP § 608.01(b).

6. In view of Applicant's amendment and response, filed 10/18/01, only the following rejections remain. The previous rejections of Claims 4 and 31-33 under the first paragraph of 35 U.S.C. § 112, and 1-7, 9-16, and 29-34 under 35 U.S.C. § 103(a) have been withdrawn.

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 31-33 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention, for the reasons of record as set forth in Paper No. 9, mailed 6/19/01.

Applicant arguments, filed 1/16/02, have been fully considered but are not found persuasive. Applicant argues that, "It is respectfully submitted that the facts of *Eli Lilly* are wholly non-analogous to the facts in the present application," followed by a brief summary of the case. It is the Examiner's position that the case is relevant in that the court found that a single species was insufficient to describe a genus encompassing ~3000-4000 species. Applicant further argues, "In marked contrast to *Eli Lilly*, in the presently rejected claims, there is unambiguous sequence information and specific procedures for determining the scope of the invention from the sequences in the specification, i.e., specific descriptions of how to determine "identity" and "hybridization under stringent conditions"." A review of the specification, however, discloses only "unambiguous sequence information" for specific constructs such as the one disclosed as SEQ ID NO:2. No "unambiguous sequence information" is provided regarding the antibodies with variable regions at least 90% identical to the variable region of UCHT-1 or antibodies about 90% as effective as UCHT-1 for binding human CD3, and no single specific method for determining sequence

identity is disclosed, indeed, the specification indicates that *any* method is sufficient. Further, while stringent hybridization conditions have been disclosed, no "tangible structural features" defining the claimed polypeptides have been recited in the claims, thus, the claims encompass polypeptides as short as a few amino acids; it is the Examiner's position then that said polypeptides have not been sufficiently described in the specification. Applicant is further advised that arguments that "there are innumerable issued U.S. patents using "identity" and "hybridizing" language similar to the present language which demonstrates that the U.S. P.T.O. has held such language to meet the requirements of 35 U.S.C.§112," are not persuasive as each application is examined by the Examiner of record on it's own merits.

9. The following are New Grounds for Rejection.

10. Claims 31-33 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for,

a recombinant immunotoxin polypeptide consisting of the polypeptide encoded by the nucleotide sequence of SEQ ID NO:2, does not reasonably provide enablement for:

A) a recombinant immunotoxin polypeptide comprising the polypeptide encoded by a nucleotide sequence which hybridizes with the nucleotide sequence of SEQ ID NO:2 under stringent hybridization conditions, or

B) a recombinant immunotoxin polypeptide comprising the polypeptide encoded by any nucleotide sequence which hybridizes to the nucleotide sequence of Claim 31 under stringent hybridization conditions, or

C) a recombinant immunotoxin polypeptide comprising an antibody having a variable region which is at least about 90% identical to the variable region of UCHT-1 and is at least about 90% as effective as UCHT-1 for binding human CD3.

The specification disclosure is insufficient to enable one skilled in the art to practice the invention as claimed without an undue amount of experimentation. Undue experimentation must be considered in light of factors including: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill in the art, the level of predictability of the art, the amount of direction provided by the inventor, the existence of working examples, and the quantity of experimentation needed to make or use the invention.

Regarding A) and B), a sequence which hybridizes to SEQ ID NO:2 would be its complementary DNA sequence. A polypeptide encoded by said complementary DNA sequence would not encode the recombinant immunotoxin of the instant claims, but rather a random collection of amino acids. Said random collection of amino acids would be unlikely to function as an immunotoxin and would thus be considered highly unpredictable. Said unpredictability would necessitate undue experimentation as there would be no particular expectation of success.

Regarding C), it is well established that changes in the amino acid sequence of the variable region of an antibody create new antibodies with highly unpredictable binding characteristics. See, for example Kussie et al. (1995, Table I) which teaches that the substitution of a single amino acid can totally ablate antigen binding. As a further demonstration of the unpredictability of substituted or mutated antibodies, see Chen et al (1995). The reference again teaches that the substitution of a single amino acid can totally ablate antigen binding (Figure 1), however, the reference additionally teaches that the same substitution in closely related antibodies can have opposite effects. The authors compared the effects of identical substitutions in related antibodies D16 and T15, and as shown in Figure 3, some substitutions increased antigen binding in one antibody while ablating it in the other. The reference serves to demonstrate the highly unpredictable nature of substituted antibodies and thus, the highly unpredictable nature of the antibody of the instant claims. Given said unpredictability, significant direction would be required to make and use the instant invention as claimed. However, the specification discloses just a single recombinant immunotoxin antibody (other than that encoded SEQ ID NO:2) with a single mutation in a residue outside the CDR antigen binding domains. Said disclosure is insufficient to enable the unlimited number of immunotoxins encompassed by Claim 33.

In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. In view of the quantity of experimentation necessary, the lack of sufficient working examples encompassing the entirety of the claimed methods, the unpredictability of the art, and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

11. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

12. Claims 1-7, 9-16, and 30-34 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically:

A) the phrases:

"A recombinant immunotoxin polypeptide and pharmaceutically acceptable salts thereof," (Claims 1-7, 9-16, and 33), or

"A recombinant immunotoxin polypeptide and the pharmaceutically acceptable salts thereof" (Claims 30-32), or

"A recombinant immunotoxin polypeptide ... and their pharmaceutically acceptable salts thereof," (Claim 34), are improper mixes of a singular polypeptide and plural salts. Additionally, the claims literally recite a composition that would consist of a polypeptide and polypeptide salts. Amending the phrases to recite "A recombinant immunotoxin polypeptide or a pharmaceutically acceptable salt thereof" would obviate the rejection.

B) Claims 10 and 11 are are incomplete because they are dependent on canceled Claim 8.

13. The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

14. Claims 1-7, 9-16, 29-30, and 33-34 are rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 6,103,235 (2000, of record) in view of Kreitman et al. (1995, of) and Kreitman et al. (1994, IDS:AS).

The '235 patent teaches a recombinant immunotoxin polypeptide (RIP) comprising a single chain Fv (which is an F_{ab} fragment) anti-human UCHT-1 CD3$\varepsilon\gamma$ binding domain and a diphtheria

toxin (DT) (an ADP-ribosylating exotoxin) (see entire document, particularly column 19 lines, 21-30). The reference further discloses a RIP pharmaceutical composition comprising a single chain Fv fused to the carboxy terminus of the exotoxin in a V_L - L - V_H - C - exotoxin conformation (see particularly Figure 12).

The reference teachings differ from the claimed invention in that they do not teach the use of PE38 as the ADP-ribosylating exotoxin in the RIP construct.

Kreitman et al. (1995) teaches immunotoxic antibody - PE38 fusion proteins and antibody - PE40 fusion proteins (see particularly, Figure 1). The reference further teaches that the PE 38 and PE40 immunotoxins are functionally interchangeable (see particularly Figure 2A).

Kreitman et al. (1994) teaches immunotoxic antibody - PE40 fusion proteins and immunotoxic antibody - DT fusion proteins, and that they are functionally interchangeable (see particularly, Figure 2 and Table 2).

From the teachings of the references it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to produce a pharmaceutical composition comprising a RIP comprising a single chain Fv (which is an F_{ab} fragment) anti-human UCHT-1 CD3$\epsilon\gamma$ binding domain, further comprising a single chain Fv fused to the carboxy terminus of the exotoxin in a V_L - L - V_H - C - exotoxin conformation (the polypeptide of SEQ ID NO:1, encoded by the nucleotide of SEQ ID NO:2), as taught by the '235 patent substituting the PE38 exotoxin for the DT exotoxin, as taught by Kreitman et al. (1994 and 1995). One of ordinary skill in the art would have been motivated to make said substitution because PE38 exotoxin was a well-known equivalent for PE40 exotoxin which was a well-known equivalent for the DT exotoxin disclosed in the '235 patent, as demonstrated by Kreitman et al. (1995 and 1994). The substitution of known equivalents is considered obvious (see MPEP 2164.06) and one of ordinary skill in the art would have a reasonable expectation of success in making said substitution. Note that the claim limitation of a PE mutant having ADP-ribosylating and translocation functions but substantially diminished cell-binding ability recited in Claim 1 merely comprises a functional characteristic of the PE38 mutant taught by Kreitman et al. (1995). Likewise, the claim limitations of claims 3-11, regarding the CD3 binding domain, e.g., an anti-CD3 binding fragment which binds an epitope on the CD3ϵ chain comprising a single chain Fv, are functional characteristics of

the UCHT-1 antibody and thus characteristics of the UCHT-1 construct of the '235 patent.

Applicant's arguments, filed 10/18/01, have been fully considered but they are not persuasive. While the previous rejection under 35 U.S.C. § 103(a) has been withdrawn, aspects of the new rejection common to both, to which Applicant has provided arguments must be addressed. However, Applicant's arguments concern the Thompson et al. reference and U.S. Patent No, 5,489,525, neither of which is used in the instant rejection. Thus, Applicant's arguments have been rendered moot.

15. No claim is allowed.

16. Only the claims of reference AM on the form 1449 filed 10/18/01 (formerly AQ on the form 1449 filed 4/13/00), have been considered because they are the only section of the reference translated into English.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Gerald Ewoldt whose telephone number is (703) 308-9805 The examiner can normally be reached Monday through Thursday and alternate Fridays from 7:30 am to 5:30 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

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March 25, 2002